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Physiological, behavioral and subjective sadness reactivity in frontotemporal dementia subtypes

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Abstract

Frontotemporal dementia (FTD), a neurodegenerative disease broadly characterized by socioemotional impairments, includes three clinical subtypes: behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA) and non-fluent variant primary progressive aphasia (nfvPPA). Emerging evidence has shown emotional reactivity impairments in bvFTD and svPPA, whereas emotional reactivity in nfvPPA is far less studied. In 105 patients with FTD (49 bvFTD, 31 svPPA and 25 nfvPPA) and 27 healthy controls, we examined three aspects of emotional reactivity (physiology, facial behavior and subjective experience) in response to a sad film. In a subset of the sample, we also examined the neural correlates of diminished aspects of reactivity using voxel-based morphometry. Results indicated that all three subtypes of FTD showed diminished physiological responding in respiration rate and diastolic blood pressure; patients with bvFTD and svPPA also showed diminished subjective experience, and no subtypes showed diminished facial behavior. Moreover, there were differences among the clinical subtypes in brain regions where smaller volumes were associated with diminished sadness reactivity. These results show that emotion impairments extend to sadness reactivity in FTD and underscore the importance of considering different aspects of sadness reactivity in multiple clinical subtypes for characterizing emotional deficits and associated neurodegeneration in FTD.

Key words: emotional reactivity; sadness; physiology; facial behavior; subjective experience; frontotemporal dementia; frontotemporal dementia clinical subtypes; voxel-based morphometry

Introduction

Frontotemporal dementia (FTD) is a neurodegenerative disease characterized by striking changes in socioemotional functioning due to frontal and anterior temporal lobe atrophy. Early manifestations of the disease include disinhibition, poor insight and reduced emotional reactivity (Boxer & Miller, 2005; Clark & Warren, 2016). In our previous studies of emotion in FTD, patients with FTD showed diminished emotional responses in situations designed to produce embarrassment (Sturm *et al.*, 2006, 2009).

However, these earlier studies characterized emotional responding in a broad spectrum of FTD syndromes and did not distinguish among the clinical subtypes. FTD has three subtypes, including behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA) and non-fluent variant primary progressive aphasia (nfvPPA). Although socioemotional functioning impairments characterize FTD broadly (Rosen *et al.*, 2002; Seeley *et al.*, 2005), each subtype has a relatively distinct pattern of neurodegeneration contributing to a different set of symptoms. In bvFTD, emotional blunting occurs due to

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atrophy in the right anterior insula and pregenual cingulate cortex; in svPPA, loss of semantic knowledge occurs due to asymmetric atrophy (generally left greater than right) in the anterior temporal lobes, and in nfvPPA, non-fluent production of speech occurs due to atrophy in the left insula, frontal operculum and inferior frontal gyrus (Seeley *et al.*, 2009). Given different neurodegeneration patterns and variations in clinical symptoms in each FTD subtype, characterizing the extent to which emotional functioning is diminished in each subtype may yield helpful diagnostic considerations.

Emotion theories and empirical data suggest that physiological responses, facial behaviors and subjective experiences are all key elements of emotional reactivity (Keltner & Gross, 1999; Mauss *et al.*, 2005; Levenson, 2014). Previous research has found clear deficits in emotional reactivity in bvFTD, including diminished physiological, behavioral and subjective responses to a disgust-eliciting film (Eckart *et al.*, 2012), diminished prosocial behavior (Sturm *et al.*, 2017, 2018b), diminished skin conductance in response to aversive odors (Perry *et al.*, 2017) and diminished skin conductance in response to task errors (Scherling *et al.*, 2017). More recent studies have found emotional reactivity impairments in bvFTD and svPPA, including diminished or incongruent responding to negative stimuli (e.g. negative emotional faces or acoustic startle) using measures of facial electromyography activity and skin conductance (Joshi *et al.*, 2014; Hua *et al.*, 2018; Marshall *et al.*, 2018; Kumfor *et al.*, 2019). Evidence for impaired reactivity in nfvPPA is emerging (e.g. reduced facial electromyography to faces and reduced pupil dilation in response to sounds; Fletcher *et al.*, 2015; Marshall *et al.*, 2018), but emotional reactivity in nfvPPA has been far less studied. Together, studies to date suggest that neurodegeneration in FTD subtypes—particularly for bvFTD and svPPA—affects negative emotion processing through multiple aspects of emotional reactivity. However, limited research has examined whether all FTD subtypes have impairments in responding to sadness-eliciting stimuli, specifically.

Sadness is a negative emotion that promotes introspection following irrevocable loss, such as losing a loved one, and serves important interpersonal functions (Lazarus, 1991). Sadness is thought to facilitate social support from others (Keltner & Kring, 1998) and may be particularly adaptive for social connection and relationships in late-life (Lwi *et al.*, 2019). Carefully assessing sadness is important in FTD subtypes given their well-documented difficulties in interpersonal realms (e.g. diminished empathy, warmth and altered humor; Rankin *et al.*, 2005; Kumfor & Piguet, 2012; Hsieh *et al.*, 2013; Clark *et al.*, 2015; Toller *et al.*, 2019). Moreover, prior studies of sadness reactivity in FTD have yielded inconsistent results. Although caregivers' observations suggest that patients with FTD may have a reduced capacity to express sadness (Snowden *et al.*, 2001), a previous study from our laboratory found no impairments in physiological, behavioral and subjective responses to a sadness-eliciting film in a combined FTD sample (Werner *et al.*, 2007).

In neurodegenerative diseases such as FTD, changes in sadness reactivity are likely caused by neurodegeneration in several regions that underlie processes for this emotion. In healthy individuals, functional neuroimaging studies have identified distributed regions, including prefrontal, cingulo-insular, temporal, ventral striatal and cerebellar areas that are more activated when participants are presented with sad autobiographical memories, pictures or films than when viewing neutral stimuli (Mayberg *et al.*, 1999; Liotti *et al.*, 2000; Habel *et al.*, 2005; Vytal & Hamann, 2010). Research suggests that each aspect of reactivity (physiology, facial behavior and subjective experience) depends on somewhat different neural networks (Hainesa *et al.*, 1984; Devinsky *et al.*, 1995; Barbas *et al.*, 2003; Critchley *et al.*, 2004; Pereira *et al.*, 2010; Craig, 2011; Uddin, 2014; Vigliocco *et al.*, 2014; Benarroch, 2015), and these different aspects are often activated together in healthy individuals in a coherent and coordinated manner (Mauss *et al.*, 2005; Levenson, 2014; Brown *et al.*, 2019). Using patient models to study neural correlates of emotional processes can offer insights into the brain regions necessary for such processes (Adolphs, 2016). Thus, careful assessment of multiple aspects of emotional responding in patients with well-characterized areas of neural loss can help determine which brain regions are critical for different aspects of sadness reactivity. Neurodegenerative diseases like bvFTD, nfvPPA and svPPA damage large-scale networks in the frontal and temporal lobes (Seeley *et al.*, 2009), offering a useful model for studying these issues. For this reason, the present study also examined atrophy associated with each diminished aspect of sadness reactivity within each FTD subtype.

The present study had two primary goals: (i) to examine whether patients with each FTD subtype have impairments in different aspects of sadness reactivity (physiology, facial behavior and subjective experience) compared to healthy controls and (ii) to identify the neural substrates underlying diminished sadness reactivity in each FTD subtype using whole-brain voxel-based morphometry (VBM) analyses. Because brain regions related to sadness reactivity are targeted in FTD (e.g. frontal and anterior temporal, cingulo-insular regions), we hypothesized that each FTD subtype would show impairments in all three aspects of sadness reactivity compared to controls. Given the lack of prior literature examining neural correlates of sadness reactivity with multiple aspects of sadness reactivity *and* three clinical subtypes of FTD, we did not cast a priori hypotheses for the second goal.

Materials and methods

Participants

Our sample included 105 patients with FTD (49 bvFTD, 31 svPPA and 25 nfvPPA) and 27 healthy controls (HCs). See Table 1 for demographic and clinical details. Participants were recruited through the Memory and Aging Center at the University of California, San Francisco (UCSF) and underwent detailed clinical interviews, neurological examination, functional assessment, neuropsychological evaluation and structural MRI. Patients were diagnosed based on current consensus criteria for FTD and its subtypes (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011). HCs were screened to ensure that they had no history of neurological, psychiatric or cognitive disorders. At the Berkeley Psychophysiology Laboratory at the University of California, Berkeley (UCB), participants underwent an assessment of emotional functioning. At UCSF and UC Berkeley, the research project (approved by the Committee on Human Research) was described to participants and they or their legal guardians provided informed consent.

Experimental design

After the UCSF visit, participants completed a daylong assessment of emotional functioning (Levenson *et al.*, 2008) at UCB (within 3 months for patients and within 12 months for HCs). To assess sadness reactivity, participants watched a scene from *The Champ* (1979) depicting a boy crying after his father dies following

Table 1. Characteristics of participants by diagnostic group

	Healthy controls	bvFTD	nfvPPA	svPPA	Statistics
n	27	49	25	31	
Age	66.13 (8.25)	60.62 (8.26)	67.82 (7.04)	63.39 (5.40)	$F(3,128) = 6.30$, $P < 0.001$; **HC > bvFTD; *nfvPPA > svPPA; ***nfvPPA > bvFTD
Handedness	25 RIGHT	44 RIGHT	22 RIGHT	30 RIGHT	$\chi 2(3,N = 132) = 1.75$, $P = 0.63$
Sex	10 M, 17 F	30 M, 19 F	17 M, 14 F	22 M, 13 F	$\chi 2(3,N = 132) = 5.19$, $P = 0.16$
Education	17.37 (2.15)	15.63 (3.07)	16.28 (3.95)	16.10 (2.70)	$F(3,128) = 1.95$, $P = 0.13$
MMSE	27.26 (8.62)	23.71 (6.09)	23.16 (8.62)	23.81 (5.31)	$F(3,128) = 4.26$, $P = 0.007$; **HC > bvFTD; **HC > svPPA; *HC > nfvPPA
CDR-Total	0 (0)	1.24 (0.65)	0.52 (0.47)	0.68 (0.42)	$F(3,128) = 39.85$, $P < 0.001$; ***HC > bvFTD; ***HC > svPPA; ***HC > nfvPPA; ***svPPA > bvFTD; ***nfvPPA > bvFTD
CDR-Box	0 (0)	6.91 (3.16)	2.08 (2.13)	3.94 (2.48)	$F(3,128) = 51.88$, $P < 0.001$; ***HC > bvFTD; ***HC > svPPA; ***HC > nfvPPA; ***svPPA > bvFTD; ***nfvPPA > bvFTD; **nfvPPA > svPPA

Means (M) and standard deviations (SD) are listed for each group, unless otherwise noted. bvFTD = behavioral variant frontotemporal dementia, nfvPPA = non-fluent variant primary progressive aphasia, svPPA = semantic variant primary progressive aphasia, MMSE = Mini-Mental State Examination, CDR Total = Clinical Dementia Rating Total score, CDR-Box = Clinical Dementia Rating Sum of Boxes, PPVT = Peabody Picture Vocabulary Test. *Post hoc* group comparisons conducted using independent sample *t*-tests with Bonferroni corrections. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

a boxing match.[1] Previous research has shown that this film clip effectively induces sadness in healthy individuals (Gross & Levenson, 1995; Seider *et al.*, 2011).[2] Participants first viewed an 'X' on the center of the screen for 60-s (pre-film baseline) and then viewed the 86-s film clip. Participants then rated their subjective experience of sadness and nine other emotions (see below) and answered a memory question about a detail of the film clip. Physiological data and video of the participants' face and torso were recorded continuously.

Measures

Cognitive functioning. Cognitive functioning was assessed at UCSF using the Mini Mental State Examination (MMSE; O'Bryant *et al.*, 2008); lower scores indicate worse cognitive functioning.

Disease severity. Disease severity was assessed at UCSF using the Clinical Dementia Rating Scale (CDR; Morris, 1993). The CDR Sum of the Boxes (CDR-Box) scores were computed for each participant; higher scores indicate greater functional impairment.

Medications. Participants' current medications were recorded at UCSF. Medications likely affecting autonomic responding (i.e. beta-blockers, beta-adrenergic agonists and anti-cholinergics) were flagged (1 = used and 0 = not used).

Memory question. To ensure participants attended to and understood the film clip, participants identified what happened in the film by choosing from three multiple choice options. Responses were coded as correct or incorrect.

Physiology. Physiological measures were monitored continuously using a Biopac polygraph, a computer with analog-to-digital capability, and an online data acquisition and analysis software package written by one of the authors (RWL). The software computed second-by-second responses for the following measures: (i) heart rate: Beckman miniature electrodes with Redux paste were placed in a bipolar configuration on opposite sides of the participant's chest—the inter-beat interval was calculated as the interval, in milliseconds, between successive R waves; (ii) finger pulse amplitude: a UFI photoplethysmograph recorded the amplitude of blood volume in the finger using a photocell taped to the distal phalanx of the index finger of the non-dominant hand; (iii) finger pulse transmission time: the time interval in milliseconds was measured between the R wave of the electrocardiogram (ECG) and the upstroke of the peripheral pulse at the finger site, recorded from the distal phalanx of the index finger of the non-dominant hand; (iv) ear pulse transmission time: a UFI photoplethysmograph attached to the right earlobe recorded the volume of blood in the ear, and the time interval in milliseconds was measured between the R wave of the ECG and the upstroke of peripheral pulse at the ear site; (v) systolic blood pressure and (vi) diastolic blood pressure: continuously recorded using an Ohmeda Finapress 2300; (vii) skin conductance: a constant-voltage device was used to pass a small voltage between Beckman regular electrodes (using an electrolyte of sodium chloride in unibase) attached to the palmar surface of the middle phalanges of the ring and index fingers of the non-dominant hand; (viii) general somatic activity: an electromechanical transducer attached to the platform under the participant's chair generated an electrical signal proportional to the amount of movement in any direction; (ix) respiration rate: a pneumatic bellow was stretched around

1 Previously reported data on sadness reactivity in FTD were collected from participants who were recruited from 2001 to 2007 (Werner *et al.*, 2007), whereas the current study reports data from participants who were recruited from 2007 to 2012 (with no overlap in participants).

2 During the emotion assessment, we also assessed amusement and disgust reactivity. Because these aspects of emotional reactivity in FTD have been analyzed and reported previously (Eckart *et al.*, 2012; Sturm *et al.*, 2015; Verstaen *et al.*, 2016), and the current study overlaps with participants from previously reported data, we did not report on these other tasks.

the thoracic region, and the inter-cycle interval was measured in milliseconds between successive inspirations. This array of measures was selected to sample from major autonomic (cardiovascular, electrodermal and respiratory) and somatic systems important for emotional responding (Sturm *et al.*, 2006; Verstaen *et al.*, 2016).

Artifacts in physiological responses were cleaned by trained research assistants and then interpolated using the adjacent clean data values. Time series of physiological responses to the film were computed by subtracting the average level of each measure during the pre-film baseline (60-s) from the average level during the entire duration of the film (86-s). To examine whether there were any time varying effects on physiological responding (e.g. between group effects may be bigger in later phases compared to early phases of the film), the 86-s film was divided into nine segments with the first segment including 6-s and the remaining eight segments including 10-s of averaged data. Baseline physiology and reactivity data are presented in Table 2.

Facial behavior. Participants' facial behavior was recorded continuously using a remote-controlled, high-resolution video camera. Trained coders rated facial behavior during an emotionally intense 30-s period of the film using the Emotional Expressive Behavior coding system (Gross & Levenson, 1993). Facial behavior was coded second by second for nine emotional behaviors (anger, disgust, happiness/amusement, contempt, sadness, embarrassment, fear, surprise and confusion) on an intensity scale ranging from 0 to 3. Sadness behavior was coded when the participant displayed upturned inner eyebrows and downturned lip corners. Inter-coder reliability for the coding system was high (intraclass correlation coefficient = 0.88). To account for emotional facial behavior not specific to sadness (e.g. amusement during the sad film), we computed a ratio of the intensity score for sadness to the total intensity score for all nine emotional behaviors. We used this ratio as an index of sadness facial behavior corrected for other emotional facial behaviors.

Subjective experience. After viewing the film, participants rated their subjective experience of sadness and nine other positive and negative emotions (affection, fear, amusement, anger, shame, disgust, embarrassment, enthusiasm and pride) during the film on a three-point scale (0 = not at all; 1 = a little; 2 = a lot). Because a previous study found patients with FTD endorse more emotions the film was not selected to induce (e.g. pride in response to a sad film) compared to controls (Chen *et al.*, 2017), we computed a ratio of the intensity of sadness endorsed to the total intensity endorsed for all 10 emotions. We used this ratio as an index of sadness subjective experience corrected for the experience of other emotions.

Neuroimaging

Participants underwent 1.5-T, 3-T or 4-T research-quality structural MRI. MRIs were included if acquired within close proximity to participants completing emotional assessments (within 12 months for HCs, within 3 months for patients). MRIs were inspected for movement artifact and poor scan quality, and nine MRI scans were excluded based on these criteria. Eight participants did not have an MRI scan. 115 MRIs were included in the neuroimaging analyses (39 bvFTD, 23 nfvPPA, 28 svPPA and 25 HCs). For details on MRI acquisition, see Supplementary Materials. For pre-processing, statistical parametric mapping version 12 default parameters were used with the light clean-up procedure in the morphological filtering step (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Structural T1 images were corrected for bias field and segmented into gray matter, white matter and cerebrospinal fluid. Because T1 images were acquired from different scanning sites, images were spatially normalized into MNI space (Ashburner & Friston, 2005) and smoothed with an 8 mm full-width at half-maximum Gaussian kernel to account for imperfection in co-registration and normalization. This approach has been used in previous publications (Sturm *et al.*, 2015; Verstaen *et al.*, 2016). Default tissue probability priors (voxel size, $2.0 \times 2.0 \times 2.0$ mm) of the International Consortium for Brain Mapping were used. Segmented images were inspected for adequate gray matter segmentation.

Analyses

Demographic and clinical variables

We used analyses of variance to compare the subtype groups to HCs in age, education, cognitive functioning (MMSE) and disease severity (CDR-Box). We used chi-square tests to determine whether there were similar proportions of men and women and left- and right-handers among the patients and HCs. Variables that showed a significant main effect of diagnosis were included as covariates in our sadness reactivity analyses.

Memory control question

We performed chi-square tests to determine whether similar proportions of patients and HCs answered the memory control question correctly.

Sadness reactivity

For physiological responding, we conducted a one-way analysis of covariance (ANCOVA) to compare responses between the subtype groups and HCs (adjusting for age, MMSE and medications). In these analyses, we accounted for possible effects of medications on physiology using a medication covariate (described above). Repeated measures ANCOVAs on averaged bins (i.e. nine-time segments) were also conducted on physiological measures to test for an interaction of diagnosis (including three subtype groups and HCs) X time (adjusting for age, MMSE and medications). For facial behavior and subjective experience, we conducted ANCOVAs to compare responding between the subtype groups and HCs (adjusting for age and MMSE). We also conducted *post hoc* group comparisons using *t*-tests with Bonferroni correction. To determine if demographic or clinical differences between the groups influenced our results, we examined the associations between physiological, behavioral and subjective aspects of sadness reactivity and age and MMSE in our ANCOVA models. If either age or MMSE was associated with an aspect of sadness reactivity, then they were included in our neuroimaging analyses as nuisance covariates.

Neuroimaging

First, we examined structural differences between the patient groups and HCs to characterize neurodegeneration. Second, we conducted whole-brain VBM analyses to examine the relationship between structural gray matter maps and each aspect of sadness reactivity within each FTD subtype (with HCs for each

Table 2. Physiological, behavioral and subjective aspects of sadness

	Baseline				Reactivity				
	Healthy controls	bvFTD	nfvPPA	svPPA	Healthy controls	bvFTD	nfvPPA	svPPA	Group comparisons for reactivity
Physiology									
Inter-beat interval (ms)	930.18 (113.68)	839.68 (140.34)	849.82 (152.13)	908.64 (150.16)	−15.67 (38.38)	4.88 (20.47)	2.15 (35.67)	−2.88 (28.83)	**HC > bvFTD
Finger pulse amplitude (units)	23.77 (24.06)	27.61 (22.51)	30.78 (26.53)	22.49 (23.07)	−1.12 (6.96)	0.97 (6.86)	−1.87 (5.28)	−0.55 (2.73)	None
Finger pulse transmission time (ms)	251.82 (20.31)	254.08 (33.61)	253.86 (35.30)	267.46 (35.79)	−0.39 (5.79)	−0.71 (8.83)	2.89 (9.70)	−2.28 (9.98)	None
Ear pulse transmission time (ms)	206.18 (57.19)	196.04 (26.16)	192.18 (32.49)	206.70 (37.84)	−1.13 (7.26)	−0.81 (6.17)	−0.52 (5.01)	0.32 (5.38)	None
Systolic blood pressure (mmHg)	153.40 (32.33)	133.79 (21.69)	145.64 (21.62)	134.53 (26.98)	5.98 (4.93)	3.97 (7.36)	3.48 (8.14)	2.73 (7.50)	None
Diastolic blood pressure (mmHg)	84.01 (14.19)	78.73 (15.97)	77.58 (18.70)	75.19 (20.96)	3.44 (3.00)	0.91 (3.22)	1.22 (4.02)	0.81 (3.21)	**HC > bvFTD; *HC > nfvPPA; **HC > svPPA
Skin conductance (microsiemens)	2.87 (1.75)	2.39 (1.61)	3.20 (2.28)	2.05 (1.50)	0.04 (.39)	0.009 (.21)	−0.04 (.14)	0.002 (.09)	None
Somatic activity (units)	0.57 (.34)	0.86 (.52)	0.78 (.44)	0.92 (.57)	−0.02 (.18)	0.003 (.37)	−.11 (.29)	−.15 (.45)	None
Inter-cycle interval (ms)	4669.44 (1062.25)	3859.24 (817.49)	3777.09 (1134.48)	3516.87 (900.14)	−1407.58 (1115.69)	−474.70 (813.15)	−480.45 (711.32)	−280.90 (625.48)	***HC > bvFTD; **HC > nfvPPA; ***HC > svPPA
Facial Behavior (sadness/total)	—	—	—	—	0.46 (.51)	0.29 (.45)	0.26 (.44)	0.22 (.41)	None
Subjective sadness (sadness/total)	—	—	—	—	0.38 (.21)	0.26 (.23)	0.33 (.17)	0.23 (.14)	*HC > bvFTD; **HC > svPPA; *nfvPPA>svPPA

Means and standard deviations (SD) for physiological data (baselines and reactivity scores adjusted from resting baseline period), facial behavior and subjective sadness. Smaller values for inter-beat interval, finger pulse amplitude, finger pulse transmission, ear pulse transmission and inter-cycle interval indicate greater reactivity during the film. Group comparisons conducted using independent sample *t*-tests with Bonferroni corrections. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$.

analysis). We included CDR-Box (which indicates patient status as all HCs' values are 0), MRI scanner field strength (two dummy variables for the three field strengths) and total intracranial volume (TIV; summing gray matter, white matter and cerebrospinal fluid volume to control for individual differences in head size) as nuisance covariates for all analyses. VBM analysis for physiology in response to the film also included our medication covariate. Images were overlaid with MRIcron (http://people.cas.sc.edu/rorden/mricron/index.html) on a Montreal Neurological Institute (MNI) average brain based on the gray and white matter templates used for pre-processing.

Following previous studies that presented results using both liberal and strict statistical thresholds (Sollberger *et al.*, 2009; Sturm *et al.*, 2013a,b; Perry *et al.*, 2014; Shany-Ur *et al.*, 2014; Kumfor *et al.*, 2015; Perry *et al.*, 2017), we present results at $P < 0.001$, uncorrected to visualize effects and also at $P_{FWE} < 0.05$ to show regions significant with strict statistical thresholds that are corrected for multiple comparisons. Our minimum cluster size was set to 200 mm^3. Five thousand permutations were run for each analysis to derive a study-specific error distribution using vlsm2 (Bates *et al.*, 2003). Combined peak and extent thresholds were used to determine the one-tailed *T* threshold for multiple comparison correction at $P_{FWE} < 0.05$. Permutation analysis is a resampling approach to significance testing. A test statistic is compared with the null distribution derived from the present study's data set and is an accurate representation of Type 1 error at $P < 0.05$ across the entire brain (Hayasaka & Nichols, 2004).

Results

Participant characteristics

As shown in Table 1, there were diagnostic differences in age, $F(3,128) = 6.30$, $P < 0.001$, and cognitive functioning, $F(3,128) = 4.26$, $P = 0.007$. The bvFTD group was younger than HCs, and all patient groups had worse cognitive functioning compared to HCs. There were no diagnostic differences in sex, $\chi^2(3,N = 132) = 5.19$, $P = 0.16$, handedness, $\chi^2(3,N = 132) = 1.75$, $P = 0.63$, or education, $F(3,128) = 1.95$, $P = 0.13$. Thus, we included age and MMSE as covariates in our sadness reactivity analyses. As expected, there were diagnostic differences in disease severity (CDR-Box), $F(3,128) = 51.88$, $P < 0.001$; patients had greater disease severity than HCs. Because sadness reactivity analyses examined diagnostic differences while accounting for cognitive functioning (another measure indicative of patient status), we did not include CDR-Box as an additional covariate.

Memory control question

The FTD subtype groups did not differ from HCs in the proportion of participants who answered the memory question correctly, $\chi^2(3,N = 132) = 5.06$, $P = 0.17$ (proportion of correct responses: 100% HCs, 96% bvFTD, 100% nfvPPA, 90% svPPA).

Sadness reactivity

Physiological responses. There were diagnostic differences in physiological reactivity for inter-cycle interval, $F(3,114) = 9.51$, $P < 0.001$, and diastolic blood pressure, $F(3,97) = 3.39$, $P = 0.02$, but not for any other physiological measure. *Post hoc* comparisons revealed that all FTD subtypes showed smaller changes in inter-cycle interval and diastolic blood pressure in response to the sad film clip compared to healthy controls. There were no differences between FTD subtypes for inter-cycle interval or diastolic blood pressure responses. Only the bvFTD group showed smaller changes in inter-beat interval in response to the film compared to HCs. See Table 2. There was no significant diagnosis X time interaction on physiological reactivity for any specific measure (Figure 1).

Subjective experience and facial behavior. There were diagnostic differences for subjective experience to the film clip, $F(3,123) = 3.66$, $P < 0.05$. *Post hoc* comparisons for subjective experience showed that the bvFTD and svPPA groups endorsed less subjective sadness compared to HCs, and the svPPA group endorsed less subjective sadness compared to the nfvPPA group.[3] There were no diagnostic differences for sadness facial behavior, $F(3,121) = 1.61$, $P = 0.19$. See Table 2 for additional details.

To determine if demographic or clinical differences between groups influenced our results, we also examined the associations between each sadness reactivity measure with age and MMSE in our ANCOVA models. No significant associations emerged; thus, we concluded that these variables played a minimal role in influencing our results and did not include them as covariates in the neuroimaging analyses.

Neuroimaging

First, we characterized neurodegeneration patterns for each FTD subtype compared to HCs. Patients with bvFTD had greater bilateral frontoinsular and cingulate atrophy, patients with nfvPPA had predominantly left insula and inferior frontal atrophy and patients with svPPA had bilateral and predominantly left anterior temporal, insular, striatum and subgenual cingulate atrophy. See Figure 2.

Second, we examined the relationship between structural gray matter maps and each aspect of diminished sadness reactivity in each FTD subtype. See Figure 3 and Table 3.

The bvFTD group showed diminished physiological reactivity (inter-beat interval, inter-cycle interval and diastolic blood pressure) and subjective sadness compared to HCs. Within bvFTD, smaller volume in left middle occipital and angular gyri, left inferior parietal gyrus, left cerebellum (crus II), right middle occipital gyrus and right cerebellum (crus I) was associated with diminished heart rate reactivity ($P < 0.001$). No regions emerged

3 To ensure that diminished subjective sadness in the patients was not due to generic amodal semantic loss, we conducted additional analyses using a measure of semantic knowledge. During the neuropsychological assessment at UCSF, semantic knowledge was assessed with a modified version of the Peabody Picture Vocabulary test (PPVT; Kramer *et al.*, 2003), which includes 16 items. For this test, the clinician says a word and the participant matches the word to a picture representing a verb, adjective, animate object, or inanimate object from 4 picture choices. Scores range from 0 to 16; lower scores indicate greater impairment in semantic knowledge. As expected, there were diagnostic differences in PPVT scores $F(3,118) = 19.13$, $P < .001$, such that the svPPA group had lower scores than the control, bvFTD, and nfvPPA groups ($P < .001$). Subjective sadness was not associated with the PPVT score within the svPPA ($t = 1.02$, $r = .20$, $P = .32$, 95% CI [−.19, .53]), bvFTD ($t = 1.19$, $r = .18$, $P = .24$, 95% CI [−.12, .44]), or nfvPPA groups ($t = .71$, $r = .15$, $P = .49$, 95% CI [−.27, .52]). Additionally, using an analysis of covariance adjusting for the PPVT, there were still significant diagnostic differences in subjective sadness $F(3,117) = 2.93$, $P < .05$. Based on these findings, we believe that diminished subjective sadness in patients are less likely due to semantic loss.

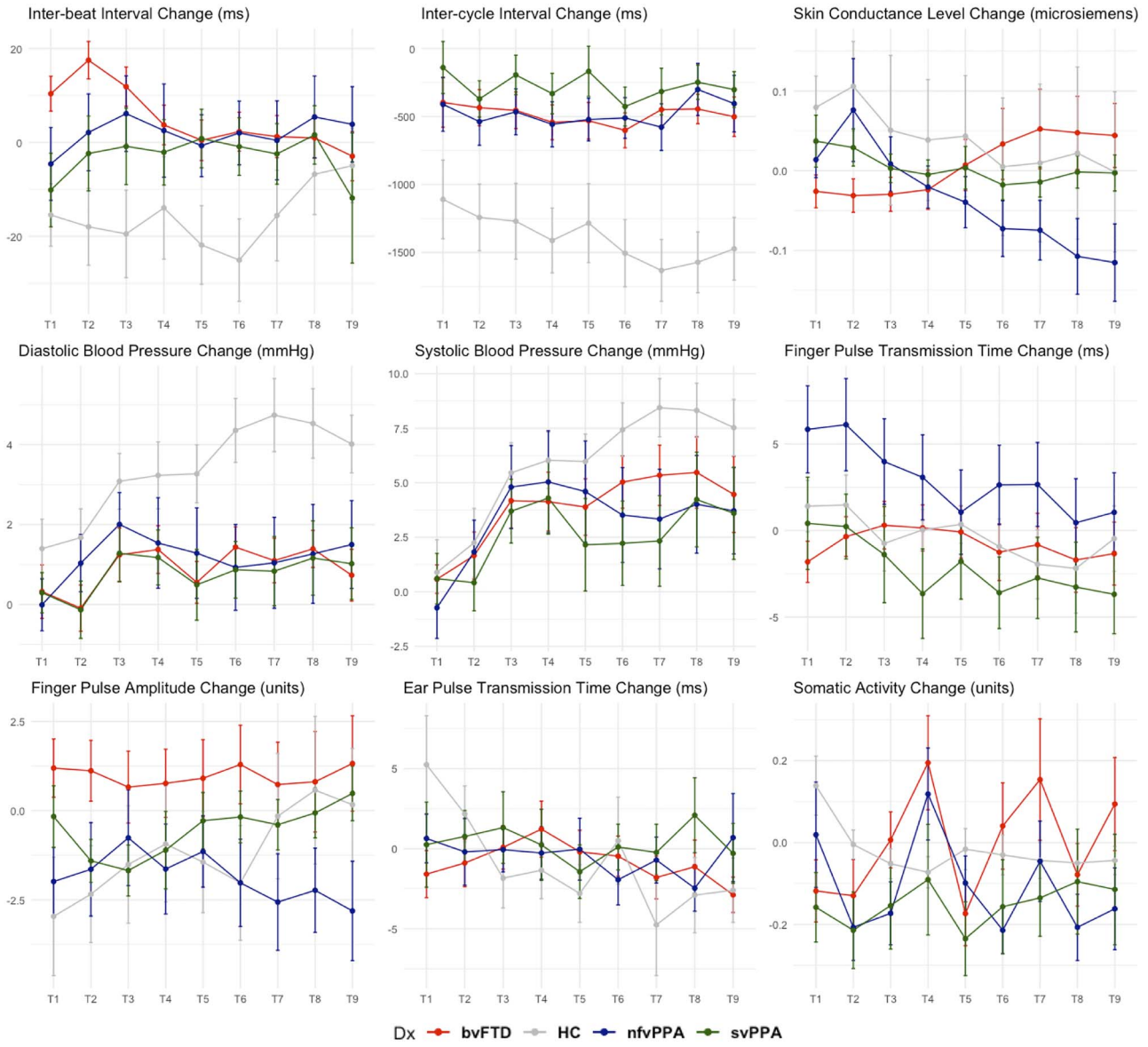

Fig. 1. Sadness Physiological Reactivity. Means and standard error bars for physiological reactivity to a sad film in patients with subtypes of frontotemporal dementia and healthy controls. The x-axis reflects averaged physiology for a 10-s bin (with the exception of the first bin which was 6-s for a full 86-s trial). There was no significant interaction of diagnosis X time. However, all FTD subtypes did show diminished inter-cycle interval and diastolic blood pressure reactivity compared to controls. The bvFTD group also had diminished inter-beat interval reactivity compared to controls. Smaller values for inter-beat interval, finger pulse amplitude, finger pulse transmission, ear pulse transmission and inter-cycle interval indicate greater reactivity during the film.

for respiration rate, diastolic blood pressure reactivity or subjective sadness within bvFTD.

The svPPA group showed diminished physiological reactivity (inter-cycle interval, diastolic blood pressure) and subjective sadness compared to HCs. Within svPPA, smaller volume in left anterior temporal regions (e.g. inferior temporal gyrus, anterior fusiform gyrus, middle temporal pole, $P_{FWE} < 0.05$) and left middle temporal gyrus regions ($P < 0.001$) was associated with diminished inter-cycle interval reactivity. No regions emerged for diastolic blood pressure reactivity or subjective sadness within svPPA.

The nfvPPA group showed diminished physiological reactivity (inter-cycle interval, diastolic blood pressure) compared to HCs. Within nfvPPA, smaller volume in the left anterior insula ($P_{FWE} < 0.05$) and right superior and middle temporal gyrus ($P < 0.001$) was associated with diminished inter-cycle interval reactivity. No regions emerged for diastolic blood pressure reactivity or subjective sadness within nfvPPA.

Discussion

The present study examined physiological, behavioral and subjective aspects of sadness reactivity in patients with three clinical subtypes of FTD and examined areas of neurodegeneration associated with diminished responding for each aspect.

Sadness reactivity

Consistent with our hypothesis, each FTD subtype showed diminished physiological responding (through respiration rate and diastolic blood pressure) compared to controls. However, inconsistent with our hypothesis of impairment across

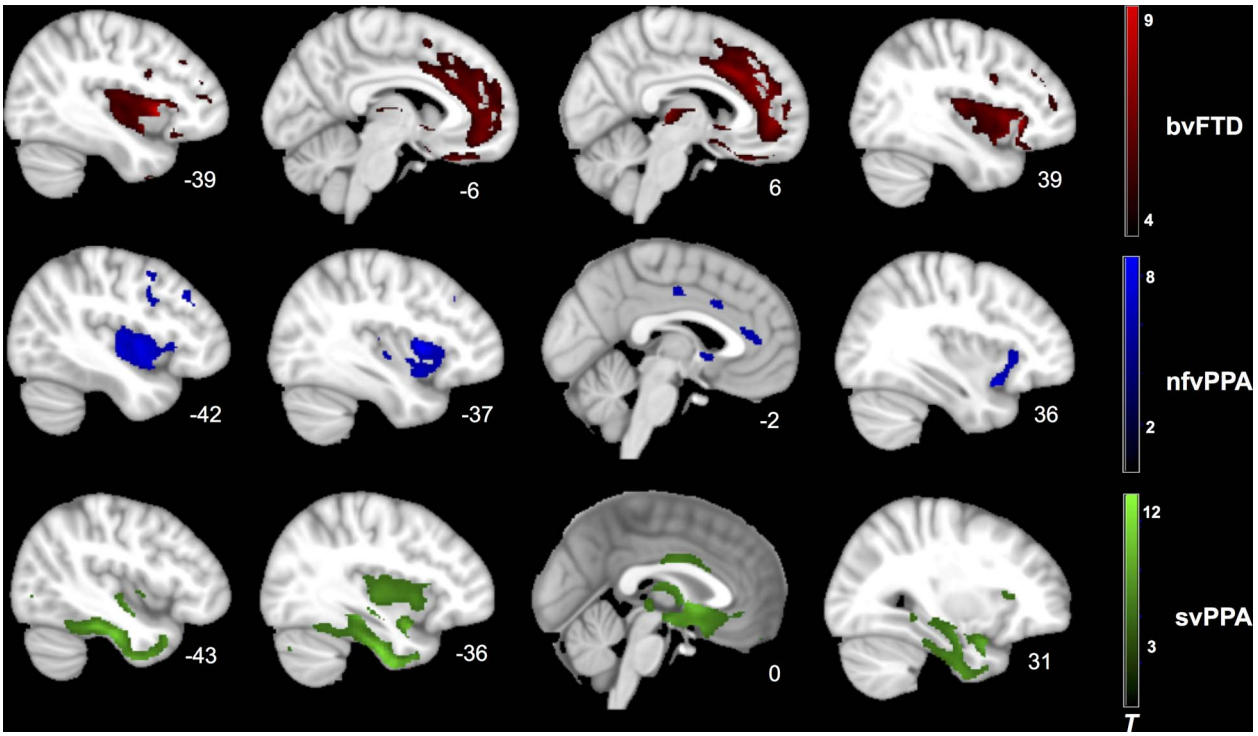

Fig. 2. Patient neurodegeneration. The atrophy pattern for each clinical FTD subtype *vs* healthy controls (bvFTD in red, svPPA in green and nfvPPA in blue). Color bar represents *T*-scores ($P_{FWE} < 0.05$) for regions with smaller volume in patient groups when adjusting for age, sex, scanner type and total intracranial volume. Patients with bvFTD had bilateral frontoinsular and cingulate atrophy; patients with nfvPPA had predominantly left insula and inferior frontal atrophy; patients with svPPA had bilateral and predominantly left anterior temporal, insular, striatum and subgenual cingulate atrophy.

Table 3. Neural correlates of diminished sadness reactivity within FTD subtypes. Results presented for each VBM analysis that looked within each FTD subtype group with healthy controls while adjusting for disease severity, scanner and total intracranial volume. Medications were included as a covariate for physiological responding. Montreal Neurological Institute coordinates (x, y, z) given for maximum *T*-score for the cluster (cluster size>200 mm^3)

Anatomical region	Cluster volume mm^3	x	y	z	Maximum *T*-score	Corrected *P*-value
bvFTD—Inter-beat interval reactivity						
Left middle occipital, angular gyrus	685	−39	−82	38	4.56	0.114
Left inferior parietal gyrus	361	−34	−74	52	4.46	0.206
Left cerebellum, crus 2	267	−10	−81	−52	3.83	0.260
Right middle occipital gyrus	263	39	−86	30	3.83	0.262
Right cerebellum, crus 1	263	14	−93	−27	4.22	0.262
Left middle occipital gyrus	226	−38	−94	4	3.92	0.292
svPPA—Inter-cycle interval reactivity						
Left inferior temporal gyrus	4350*	−48	−21	−26	4.11	0.017
Left anterior fusiform gyrus						
Left middle temporal pole						
Left middle temporal gyrus	462	−54	−26	−10	3.80	0.220
Left middle temporal gyrus	216	−60	−9	−15	3.96	0.402
nfvPPA—Inter-cycle interval reactivity						
Left anterior insula	2302*	−42	2	−8	4.38	0.031
Right superior/middle temporal gyrus	381	60	−14	8	4.00	0.273

Results considered significant at $P < 0.001$

*Results considered significant at $P_{FWE} < 0.05$

No regions emerged for inter-cycle interval reactivity, diastolic blood pressure reactivity or subjective sadness within bvFTD, diastolic blood pressure reactivity or subjective sadness within svPPA and diastolic blood pressure reactivity or subjective sadness within nfvPPA.

subtypes, there was variability in other aspects of sadness reactivity based on subtype. Compared to controls, the bvFTD group showed diminished responding in heart rate, and the svPPA and bvFTD groups showed diminished subjective experience. No subtype differences were found for sadness facial behavior or for other physiological measures.

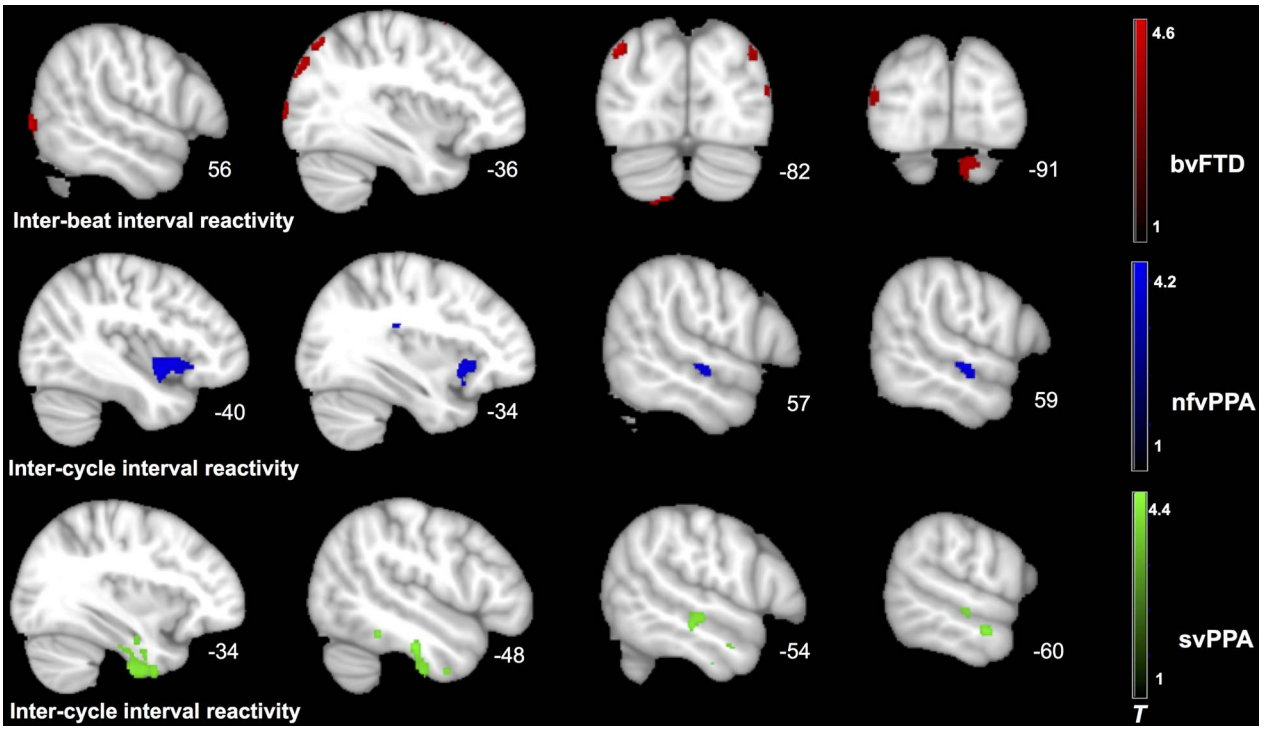

Fig. 3. Neural correlates of sadness reactivity within FTD subtypes. *T*-score maps of brain areas in which smaller gray matter volume was associated with diminished sadness reactivity to the sad film clip when adjusting for CDR-Box, field strength and total intracranial volume within each subtype group. Medications were included as a covariate for physiological measures. Within bvFTD, smaller volume in left middle occipital and angular gyri, left inferior parietal gyrus, left cerebellum (crus II), right middle occipital gyrus and right cerebellum (crus I) was associated with diminished inter-beat interval reactivity ($P < 0.001$). Within svPPA, smaller volume in left anterior temporal regions (e.g. inferior temporal gyrus, anterior fusiform gyrus, middle temporal pole, $P_{FWE} < 0.05$) and left middle temporal gyrus regions ($P < 0.001$) was associated with diminished inter-cycle interval reactivity. Within nfvPPA, smaller volume in the left anterior insula ($P_{FWE} < 0.05$) and right superior and middle temporal gyrus ($P < 0.001$) was associated with diminished inter-cycle interval reactivity.

We found common physiological impairment across FTD subtypes. Prior studies have detected impairments in emotional reactivity in bvFTD and svPPA using skin conductance (Joshi *et al.*, 2014; Sturm *et al.*, 2018b; Kumfor *et al.*, 2019). Our study suggests that other physiological measures (e.g. respiration rate and diastolic blood pressure) may be particularly useful in detecting reactivity impairments in all FTD subtypes, including nfvPPA. We also did not detect differences between groups in the temporal dynamics of physiological reactivity. Additionally, we found varying impairment in subjective experience of sadness; diminished experience of sadness in bvFTD and svPPA may underlie their more pronounced interpersonal difficulties, whereas relatively preserved emotional experiences in nfvPPA may explain, in part, their having less severe interpersonal difficulties (Takeda *et al.*, 2019). Lastly, we did not detect impairments in sadness facial behavior across subtypes. It is possible that our method of coding facial behavior was not able to detect the kinds of subtle impairments in facial expression found in bvFTD, svPPA and nfvPPA in studies using facial electromyography (Hua *et al.*, 2018; Marshall *et al.*, 2018; Kumfor *et al.*, 2019). The complexities of our findings highlight the importance of examining multiple aspects of emotional reactivity and multiple clinical subtypes of FTD when studying the impact of this disease on emotional functioning.

The present study examined emotional reactivity for a single emotion, sadness, which limits our ability to determine whether impairments found for sadness reactivity in FTD would be found for other emotions. However, previous research suggests that our findings for sadness likely reflect a more generalized impairment in negative emotional reactivity in FTD. Prior studies have found diminished disgust reactivity in bvFTD (Eckart *et al.*, 2012) and diminished embarrassment reactivity in a sample of patients with the three FTD subtypes (Sturm *et al.*, 2009). In contrast, reactivity in amusement, a positive emotion, was found to be preserved, yet variable, across the three FTD subtypes (Sturm *et al.*, 2015). We investigated sadness because this emotion may be particularly important for late-life social relationships and connection (Lwi *et al.*, 2019) and because it has only been investigated in FTD once before[4]. Although findings from the present study and previous research suggest that negative emotional reactivity may be impacted more in FTD than positive emotional reactivity, future research is needed to determine if impairment extends to other negative (e.g. fear and anger) and positive (e.g. pride) emotions.

Neural substrates

Within bvFTD, damage to distributed areas (cerebellum, angular, occipital and inferior parietal gyri) was associated with diminished heart rate increases to the sadness film. Autonomic dysfunction, in both sympathetic and parasympathetic activity,

4 In a previous study from our laboratory, we did not find evidence of diminished sadness reactivity in FTD (Werner *et al.*, 2007). However, this earlier study was conducted with a smaller sample size (28 patients with FTD and 16 controls) and may have been underpowered to detect diminished sadness reactivity.

has been found in bvFTD (Joshi *et al.*, 2014; Guo *et al.*, 2016a; Sturm*et al.*, 2018a). Heart rate is influenced by both branches of the autonomic nervous system; thus, diminished cardiovascular reactivity in response to a sad film may reflect dysregulated autonomic systems. The cerebellum is also important for salience functioning in bvFTD (Guo *et al.*, 2016b) as well as autonomic response generation (Schmahmann & Caplan, 2005). Salience network and autonomic nervous system disruption may lead to diminished heart rate increases to a sad film in bvFTD. Furthermore, hypometabolism in inferior parietal areas has been found in more apathetic types of bvFTD patients (Morbelli *et al.*, 2016). Pathology in bvFTD can show in posterior regions, including the angular gyrus, visual cortex and sensory cortex (Brettschneider *et al.*, 2014), suggesting that pathology spreads along axonal pathways from anterior to posterior regions of the brain. Damage to these more posterior regions associated with diminished heart rate reactivity may reflect emotional reactivity losses with more severe disease progression and apathy in bvFTD.

Within svPPA, damage to anterior and middle temporal regions (inferior temporal, fusiform gyrus, temporal pole and middle temporal gyrus) was associated with diminished respiration rate increases to the sadness film. Although not hypothesized, diminished respiration rate reactivity to the sad film was found in the svPPA group. In healthy adults, increased respiration rate is a robust response to negative emotional stimuli (e.g. sad films, disgusting films or negative self-beliefs; Seider *et al.*, 2011; Goldin *et al.*, 2019). Because increased respiration rate is a typical response to negative emotional stimuli, diminished respiration rate reactivity in svPPA may reflect problems in emotional processing. Damage to anterior temporal regions associated with widespread network dysfunction, interference with interpersonal warmth and impaired emotion recognition (particularly for negative emotions) are well documented in svPPA (Rankin *et al.*, 2006; Guo *et al.*, 2013; Fittipaldi *et al.*, 2019). Moreover, inferior temporal and fusiform gyri have been shown to process semantic information and integrate representations of emotional information in context (Binney *et al.*, 2010; Milesi *et al.*, 2014; Pobric *et al.*, 2015). Given associations between regions important for social representation, negative emotion recognition and respiration rate, damage to regions important for social representation and recognizing negative emotional information may impact respiration rate responding to the sadness film in svPPA. Further research in svPPA is needed to determine if respiration rate is particularly sensitive to disease-related changes in emotional reactivity.

Within nfvPPA, damage to the left anterior insula and superior/middle temporal gyri was associated with diminished respiration rate increases to the sadness film. Although specific emotional impairments are less often characterized in nfvPPA, apathy and loss of empathy have been documented in this group (Van Langenhove *et al.*, 2016; Cosseddu *et al.*, 2019). Damage to the left anterior insula has also been linked to disrupted empathy and prosocial behavior in bvFTD (Hua *et al.*, 2018; Sturm *et al.*, 2018b), and damage to bilateral insula is associated with impaired recognition of emotional facial expressions in nfvPPA (Couto *et al.*, 2013). In nfvPPA, damage to the left insula is also associated with diminished cardiac sympathetic activity during an emotion identification task (Marshall *et al.*, 2019). It is possible that diminished respiration rate reactivity to the sad film may be related to autonomic dysfunction in nfvPPA during emotion processing. Moreover, superior and middle temporal gyri are important for representing social concepts and action as well as communicating with the insula (Carr *et al.*, 2003; Zahn *et al.*, 2007). Impaired empathy, social representation and autonomic dysfunction processes may underlie the nfvPPA group's diminished respiration responding to the sadness film. However, similar to the svPPA group, additional research on autonomic dysfunction and respiration rate during emotional processing in nfvPPA is needed to understand these complex neurophysiological relationships more fully.

Although we did not find neural correlates for all diminished aspects of sadness reactivity in FTD subtypes, our findings highlight how sadness reactivity breaks down in different ways within each subtype. Different aspects of sadness reactivity may depend on different neural networks (Levenson, 2007), and disrupted neural networks in each subtype lead to somewhat differentiated impairments in emotional reactivity in FTD subtypes (Seeley *et al.*, 2009). We also found that physiological measures were fruitful in detecting FTD subtype-specific neural correlates for diminished physiological aspects of sadness reactivity.

Strengths and limitations

Our study has a number of strengths, including measuring multiple aspects of sadness reactivity, accounting for behaviors and responses not specific to sadness (e.g. amusement during the sad film), including a relatively large sample of patients with adequate neuroanatomical heterogeneity, and utilizing whole-brain VBM analyses without biasing the scope of findings to specific regions-of-interest.

The study also has limitations. First, we examined sadness, an interpersonal emotion, by having participants view a film clip. Future studies should examine sadness in more interpersonal contexts (e.g. in interactions between patients and family members). Second, we examined emotional reactivity using a single sadness-eliciting film clip. Thus, we cannot know if findings generalize to other sadness films or to other emotions. Given previous findings that diminished disgust reactivity is associated with insular atrophy (Verstaen *et al.*, 2016) and diminished embarrassment reactivity is associated with pregenual cingulate atrophy (Sturm *et al.*, 2013a), the present findings highlight both similar (insula) and different regions (fusiform gyrus and anterior temporal structures) that may be important for sadness reactivity for different FTD subtypes.

Conclusions

The present study offers new insights into impairments in physiological, behavioral and subjective aspects of sadness reactivity in three clinical subtypes of FTD and associated neural substrates. We offer evidence that all FTD subtypes have diminished aspects of physiological sadness reactivity (e.g. respiration rate and diastolic blood pressure) but only svPPA and bvFTD also have diminished sadness subjective experience. We identified distinct brain regions where damage was associated with diminished physiological aspects of sadness reactivity for each FTD subtype. The present study has implications for informing basic affective neuroscience concerning the neural circuitry that is associated with different aspects of sadness and for understanding impairments to sadness that occur in clinical illness.

Supplementary material

Supplementary material is available at *SOCAFN* online.

Conflict of interest. None declared.

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